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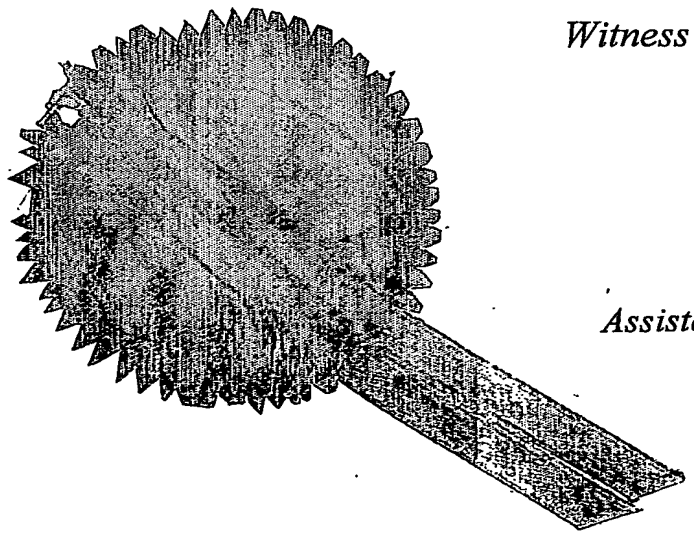
सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***1048/Del/2003 dated 28th August 2003.***

Witness my hand this 13th day of July 2005.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

chemistry
C07D243/06
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C07D243/14

1018 DEL 03

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR PREPARATION OF 1,4-BENZODIAZEPINE DERIVATIVES"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. CHANDRA HAS KHANDURI

c. MUKESH KUMAR SHARMA

d. ATULYA PANDA

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We, YATENDRA KUMAR, CHANDRA HAS KHANDURI, MUKESH KUMAR SHARMA, ATULYA PANDA of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (YATENDRA KUMAR)

b. 25/08/03
(CHANDRA HAS KHANDURI)

c. 25/08/03
(MUKESH KUMAR SHARMA)

d. 25/08/03
(ATULYA PANDA)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
   a. Complete Specification (3 copies)
   b. Drawings (3 copies)
   c. Priority document(s)
   d. Statement and Undertaking on FORM – 3
   e. Power of Authority (Not required)
   f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **25TH** day of **August, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR PREPARATION OF 1, 4-BENZODIAZEPINE DERIVATIVES

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

An improved process for the preparation of 1,4-benzodiazepine derivatives is provided.

1,4 benzodiazepine derivatives such as clorazepate are useful for the treatment of anxiety disorders. Several processes have been reported for the preparation of 1,4 benzodiazepine derivatives of formula I, including 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid i.e. clorazepate, such as in US 3,657,223, US 4,051,127, GB 1117200, EP 22710 and ES 428622.

US 3,516,988 discloses a process for the preparation of 1,4 benzodiazepine including ethyl clorazepate, comprising reacting an ortho-aminoarylketimine with anhydrous lower aliphatic acid or mineral acid. *J. Org. chem. 1973, 38, 449-456* describes the synthesis of ethyl clorazepate by reducing ethyl 2'-benzoyl-4-chloromesoxalanilate-2-oxime with zinc dust and acetic acid and further refluxing the residue, obtained after workup, in benzene in the presence of acetic acid to obtain ethyl clorazepate. It further discloses the synthesis of ethyl 2'-benzoyl-4-chloromesoxalanilate-2-oxime by nitrosating ethyl 2'-benzoyl-4-chloromalonilate with sodium nitrite in acetic acid.

In one aspect, there is provided a process for the preparation of 1,4 benzodiazepine derivative of formula I, as shown in the accompanied drawings, wherein R represents hydrogen, alkyl of C_1-C_5, aryl or arylalkyl; R^1 represents hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkoxy, nitro or amino groups; and R^2 represents furyl, thienyl, cyclohexyl, lower alkyl or phenyl, which may be substituted by halogen atom, trifluoromethyl, nitro, lower alkyl or lower alkoxy groups; in a single step comprising reacting an oxime of formula II, as shown in the accompanied drawings, wherein R, R^1 and R^2 are as defined above, with a reducing agent, in the presence of an acid catalyst at a temperature of not less than 35°C. Thus the reduction of the oxime of formula II, and cyclization to get the compound of formula I are achieved simultaneously.

In a further aspect, a process for preparing the compound of formula II, as shown in the accompanied drawings, is provided, comprising nitrosation of an amide of formula III, as shown in the accompanied drawings, wherein R, R^1 and R^2 are as defined above, with sodium nitrite in the presence of a strong inorganic acid.

Nitrosation reaction to obtain oxime of formula II is faster in the presence of a strong acid and side reactions or decomposition of product are minimized. The reaction was found to equilibrate and not go to completion in the presence of a weak acid such as acetic acid.

In some particular examples R represents methyl or ethyl, R^1 represents chlorine and R^2 represents phenyl in the compounds of formula I, II and III.

The reducing agents used for the preparation of compound of formula I are those customarily used in organic chemistry for reducing oximes selectively, such as metal/acids and hydrogenation catalysts. For example, transition metals such as Zn, Fe, and Sn used with acid such as hydrochloric acid, acetic acid and formic acid may be employed as the metal/acid reducing agents.

Examples of hydrogenation catalysts include transition metals or compounds thereof such as raney nickel and rhodium complexes used in the presence of hydrogen. The reduction may be carried out at normal pressure, or at elevated pressure depending on the choice of catalyst. In some particular embodiments, it may be carried out at a hydrogen pressure of 1-7 Kg/cm^2.

Examples of acid catalyst include organic and inorganic acids, for example, carboxylic acids such as formic acid, acetic acid and propionic acid and inorganic acids such as hydrochloric acid, hydrobromic acid and mixtures thereof.

The acid used in the metal/acid combination used as the reducing agent may also play the role of the acid catalyst.

The reaction of compound of formula II to obtain the compound of formula I may be carried out in the presence of a suitable solvent. Suitable solvents for the reaction are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include ethers such as diethylether, diisopropylether and dimethoxyethane; alcohols such as methanol, ethanol, isopropanol and butanol; ketones such as acetone and methyl isobutyl ketone; nitriles such as acetonitrile; chlorinated hydrocarbons such as methylene chloride, ethylene dichloride and carbon tetrachloride; esters such as ethylacetate and

isopropylacetate; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; cyclic ethers such as dioxane and tetrahydrofuran; and mixtures thereof.

Alternatively, the acid catalyst used in the process also serves as the solvent.

The reaction may be carried out at a temperature range from about 35°C to about 75°C. In some particular example it may be carried out at a temperature range from about 50°C to about 65°C. The reaction mixture may be stirred for 3 to 5 hours.

Compounds of formula I may be converted to compounds of formula IV, as shown in the accompanied drawings, wherein M represents an alkali metal and R_1 and R_2 are as defined above, by method known in the art such as reacting compound of formula I with alkali metal hydroxide in the presence of an alcohol. Examples of alkali metal include lithium, sodium and potassium. Examples of alcohol include methanol, ethanol, isoprapanol, butanol and mixtures thereof.

Examples of inorganic acid used in nitrosation of the compound of formula III to obtain the compound of formula II include hydrochloric acid, hydrobromic acid, hydrogenthiocyanide and mixtures thereof.

The nitrosation reaction may be carried out in the presence of suitable solvent. Suitable solvents for the reaction are inert organic solvents that do not change under the reaction conditions in combination with water. Examples of such solvents include ethers such as dimethoxyethane, dioxane and tetrahydrofuran; alcohols such as methanol, ethanol, isopropanol and butanol; chlorinated hydrocarbons such as methylene dichloride and ethylenedichloride; esters such as ethylacetate and isopropylacetate; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; and mixtures thereof.

Compounds of formula III can be produced by conventional procedures such as those reported in *J. Org. chem. 1973; 38, 449-456.*

In the following section preferred embodiments are described by way of examples to illustrate the process. However, these are not intended in any way to limit the scope of the

claims. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Example -1

Preparation of methyl 2'-benzoyl-4-chloromesoxanilate

A solution of sodium nitrite (238g) in water (420 ml) was added slowly to a vigorously stirred suspension of methyl 2' benzoyl-4-chloromalonanilate (140g) in denatured spirit (1400ml) and concentrated hydrochloric acid (700ml). After stirring for 2 hours, the product was isolated by cooling and filtration, and washed with water to remove salts. The wet material was washed with toluene (980 ml) and dried to obtain 126g of the title compound.
(HPLC Purity = 99.31%)

Example -2

Preparation of ethyl 2'-benzoyl-4-chloromesoxanilate

A solution of sodium nitrite (228.6g) in water (420 ml) was added slowly to a vigorously stirred suspension of ethyl 2' benzoyl-4-chloromalonanilate (140g) in denatured spirit (1400ml) and concentrated hydrochloric acid (700ml). After stirring for 2 hours, the product was isolated by cooling and filtration, and washed with water to remove salts. The wet material was washed with toluene (980 ml). On drying about 123g of title compound was obtained.
(HPLC Purity = 99.69%)

Example –3

Preparation of methyl ester of clorazepate

To acetic acid (1300 ml) were added methyl 2'-benzoyl-4'-chloromesoxalanilate (175g) and activated Raney Nickel (93g) and stirred. Hydrogen pressure (5.0 kg/cm^2) was then applied

to the reaction mixture and heated to 53 ^{0}C. The reaction was continued for 3 to 5 hours at 2 to 5 Kg/cm^2. After the reaction was over, the reaction mixture was filtered and acetic acid was recovered (about 70%). The title product was isolated by cooling the concentrate and filtration of the precipitate obtained, which was then washed with water. On drying about 125 g of product was obtained.
(HPLC Purity = 99.26%)

Example –4

Preparation of ethyl clorazepate

To acetic acid (1300 ml) was added ethyl 2'-benzoyl-4'-chloromesoxalanilate (175g) and activated Raney Nickel (93g) and stirred. Hydrogen pressure (5.0 kg/cm^2) was then applied to it and heated to 62 ^{0}C. The reaction was continued for 3 to 5 hours at 2 to 5 Kg/cm^2. After the reaction was over, the reaction mixture was filtered and the solvent was recovered (about 70%). The product was isolated by cooling the concentrate and filtration of the precipitate obtained, which was then washed with water. On drying about 118.5g of the product was obtained.
(HPLC Purity = 99.22%).

WE CLAIM:

1. A process for preparation of 1,4 benzodiazepine derivative of formula I, as shown in the accompanied drawings, wherein R represents hydrogen, alkyl of C_1-C_5, aryl or arylalkyl; R^1 represents hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkoxy, nitro or amino group; and R^2 represents furyl, thienyl, cyclohexyl, lower alkyl or phenyl, which may be substituted by halogen atom, trifluoromethyl, nitro, lower alkyl or lower alkoxy group; in a single step comprising reacting an oxime of formula II, as shown in the accompanied drawings, wherein R, R^1 and R^2 are as defined above, with a reducing agent, in the presence of an acid catalyst at a temperature of not less than 35°C.
2. The process according to claim 1 further comprising converting the compound of Formula I to a salt of Formula IV, as shown in the accompanied drawing, wherein M represents an alkali metal acid R^1 and R^2 are as defined above.
3. A process for preparation of compound of formula II, as shown in the accompanied drawings, wherein R, R^1 and R^2 are as defined above comprising nitrosating an amide of formula III, as shown in the accompanied drawings, wherein R, R^1 and R^2 are as defined above with sodium nitrite in the presence of a strong inorganic acid.
4. The process according to claim 1 or 3, wherein R represents methyl or ethyl, R^1 represents chlorine and R^2 represents phenyl.
5. The process according to claim 1, wherein reducing agent is selected from the group consisting of metal/acids and hydrogenation catalysts.
6. The process according to claim 5, wherein a transition metal, selected from the group consisting of Zn, Fe, and Sn is used in the metal/acid combination.
7. The process according to claim 5, wherein an acid, selected from the group consisting of hydrochloric acid, acetic acid and formic acid is used in the metal/acid combination.
8. The process according to claim 5, wherein the hydrogenation catalyst is a transition metal, selected from the group consisting of Raney nickel and a rhodium complexes used in the presence of hydrogen gas.
9. The process according to claim 8, wherein the reduction is carried out at a pressure of from 1.0 to 7.0 kg/cm^2 of hydrogen gas.
10. The process according to claim 1, wherein the reaction is carried out in the presence of suitable solvent selected from the group consisting of ethers, alcohols, chlorinated,

hydrocarbons, esters, cyclic ethers, ketones, nitriles, dipolar aprotic solvents and mixtures thereof.

11. The process according to claim 10, wherein the alcohol is selected from the group consisting of methanol, ethanol, isoprapanol, butanol and mixtures thereof.
12. The process according to claim 1, wherein acid catalyst is selected from the group consisting of organic acid and inorganic acids,
13. The process according to claim 12, wherein the organic acid is selected from the group consisting of acetic acid, formic acid, propionic acid and mixtures thereof.
14. The process according to claim 12, wherein the inorganic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid and mixtures thereof.
15. The process according to claim 1, wherein the reaction is carried out at a temperature range from about 35°C to about 75°C.
16. The process according to claim 3, wherein inorganic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydrogenthiocyanide and mixtures thereof.
17. The process according to claim 3, wherein the reaction is carried out in the presence of a suitable organic solvent in combination with water.
18. The process according to claim 17, wherein the organic solvent is selected from the group consisting of ethers, alcohols, chlorinated hydrocarbons, esters, dipolar aprotic solvents and mixtures thereof.
19. The process according to claim 18, wherein the alcohol is selected from the group consisting of methanol, ethanol, isoprapanol, butanol and mixtures thereof.
20. The process according to claim 1, wherein the oxime of formula II is prepared by the process as claimed in claim 3.
21. The process for preparing compound of formula I, as herein described and illustrated by the examples herein.

Dated **25TH** day of **August, 2003.**

For Ranbaxy Laboratories Limited

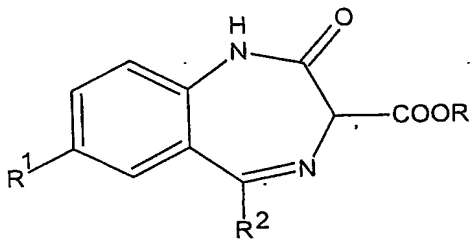
(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

Application No.

No. of sheets = 04

Sheet 01 of 04



Formula I

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

DEL 05

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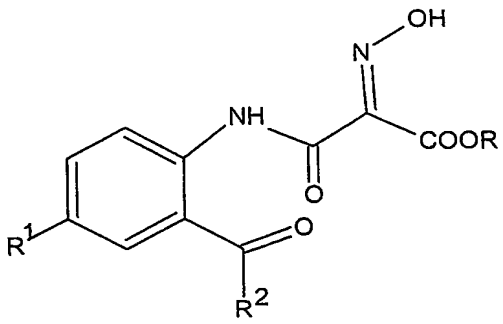
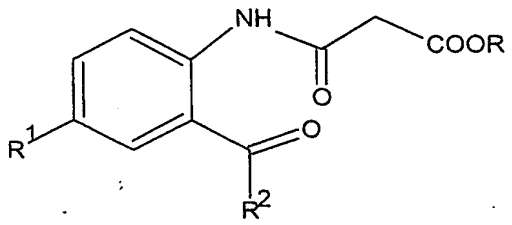


Formula II

For Ranbaxy Laboratories Limited

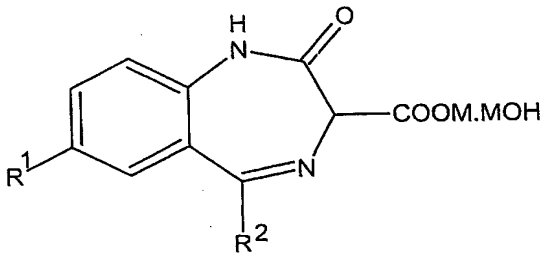
(Sushil Kumar Patawari)
Company Secretary



Formula III

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



Formula IV

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IB04/002775

International filing date: 27 August 2004 (27.08.2004)

Document type: Certified copy of priority document

Document details: Country/Office: IN
Number: 1048/DEL/2003
Filing date: 28 August 2003 (28.08.2003)

Date of receipt at the International Bureau: 05 December 2005 (05.12.2005)

Remark: Priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)

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Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse